The GLP-1 agonist Exendin-4 decreases responding to incentive cues

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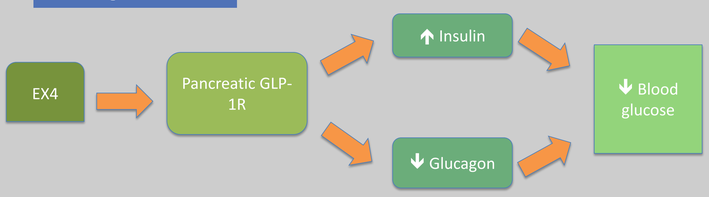
Abstract

Exendin-4 (EX4) is a glucagon-like peptide-1 (GLP-1) agonist prescribed to treat type-2 diabetes, and works primarily by increasing insulin in response to eating. EX4 additionally promotes weight loss, partially through the effects of GLP-1 receptors in the brain that regulate appetite and motivation systems. We and others have shown that EX4 decreases both the amount of food a rat will consume and the motivation to obtain palatable foods. EX4 and other GLP-1 agonists may also activate GLP-1 receptors (GLP-1R) in the mesolimbic dopamine pathway and decrease dopamine neurotransmission, which is critical for reward seeking and responding to reward associated cues. Mesolimbic dopamine may mediate processes attributing previously neutral cues (e.g. a tone or light) with appetitive properties of a reward when repeatedly paired with it. These incentive cues then promote reward seeking behaviors. In this study, we sought to determine if EX4 decreases reward seeking by reducing the response to incentive cues using an operant model of incentive cue responding for sucrose. These data will help define the behavioral mechanisms by which EX4 promotes weight loss, and could have implications for over-eating disorders and others that have a strong incentive cue component, such as substance use disorder.

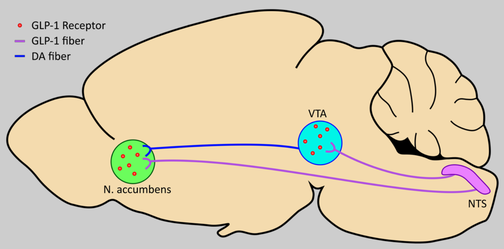
Introduction

- EX4 is a diabetes drug that lowers blood glucose levels.
- EX4 can also produce weight loss, potentially through both peripheral and central mechanisms.

Peripheral



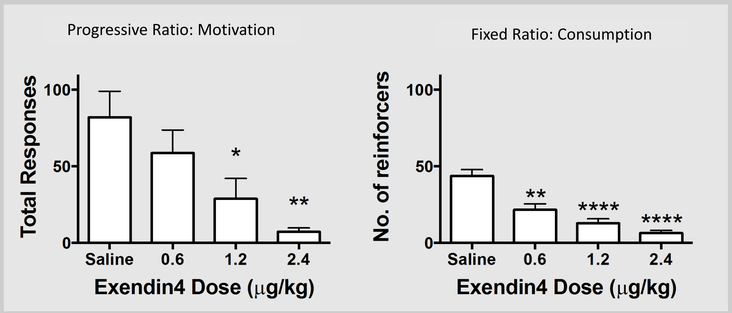
Central

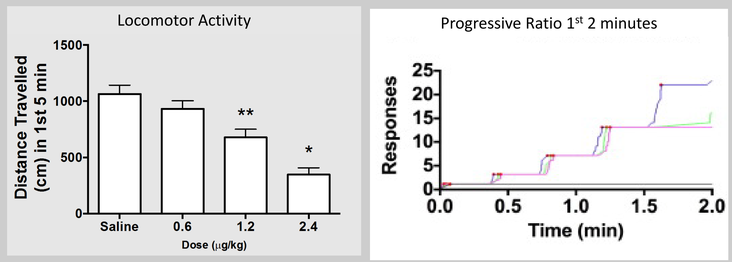


GLP-1 receptors in the mesolimbic "reward" pathway.

Background

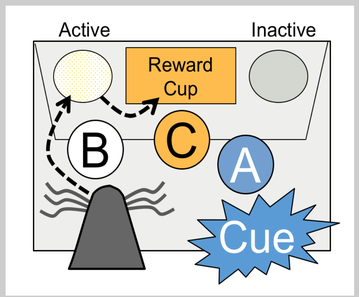
- EX4 decreases both consumption and motivation for a sweet-fat reward in an operant self-administration model.
- EX4 also decreases locomotor activity at doses from 0.6 - 2.4 µg/kg.

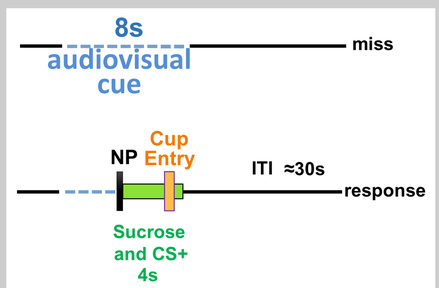




- Much less is known about how EX4 affects responding to cues that predict reward.
- Repeated pairing of a previously neutral cue with a reward can lead to the cue acquiring incentive motivational properties of the reward.
- Such incentive cues may promote and enhance subsequent reward seeking behaviors, and likely contribute to food and drug addictions.

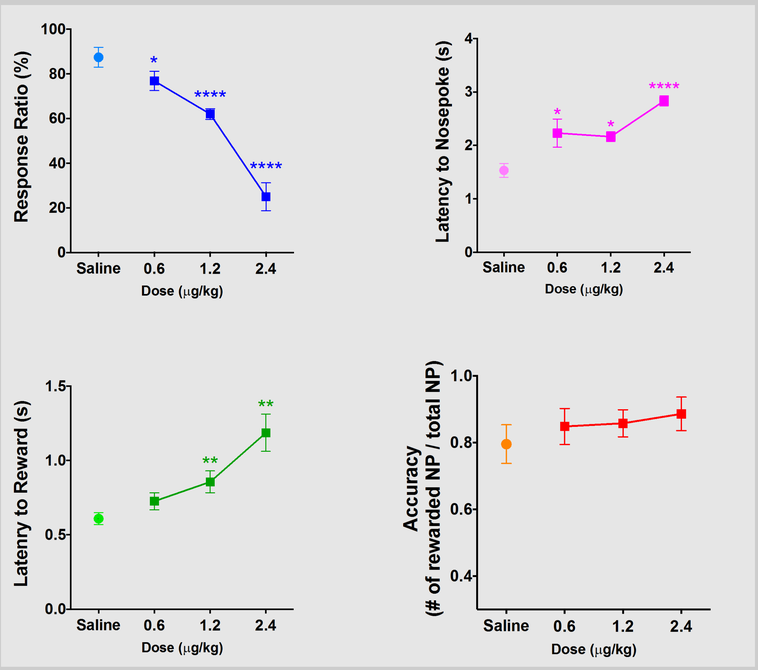
Approach





EX4 will decrease responding to incentive cues predictive of a food reward.

Results



* p < 0.05, ** p < 0.01, **** p < 0.0001

Summary

- EX4 dose-dependently decreased responding to incentive cues.
- EX4 also increased the latencies to nosepoke and reward.
- Together these data indicate that EX4 decreases both the motivational properties of the primary reward (e.g. sucrose) and the incentive cue.
- Generalized locomotor suppression does not fully account for these findings, as the 0.6 mg/kg dose was effective at suppressing responding to incentive cues but not operant responding in previous studies.

Future Directions

- Analyze the latencies from the beginning and end of the session to determine if satiety plays a role.

References

Bernosky-Smith K.A., Stranger D.B., Trujillo A.J., Mitchell L.R., Espana R.A., Bass C.E. **The GLP-1 agonist exendin-4 attenuates self-administration of sweetened fat on fixed and progressive ratio schedules of reinforcement in rats.** *Pharmacology Biochemistry and Behavior, Volume 142, March 2016, Pages 4-55*